Kidney Embryology

Introduction

There are two main goals of this lesson. The first is to reiterate the embryonic distinction between the urinary drainage system (collecting ducts, calyces, pelvis, ureter, and bladder, comes from endoderm) versus the urinary generation system (nephrons, renal columns, cortex, comes from metanephric mesenchyme). The second is to discuss congenital defects of the kidneys. While the discussion of kidney embryogenesis necessitates a discussion of bladder embryogenesis, we've chosen this lesson to focus specifically on the defects that occur in the ureters and kidneys, reserving a discussion on congenital defects that involve the ureters, bladder, and urethra for another lesson (Bladder #1: *Normal Bladder*).

As with any discussion of embryology, there is a progression of structures. We're going to show you which structures you need to be aware of. "Be aware of" means you need to know what a structure does at the stage of development in which it exists, know from what structure it was derived, and know what structures it will develop into.

Finally, a brief overview. Throughout embryogenesis there are three structures that handle water waste. The pronephros develops first, and quickly disappears. The mesonephros is the functional filtration unit for most of embryogenesis. The metanephros is the developing kidney. They are three distinct structures. Water waste is mostly handled by the umbilical cord. Water, amniotic fluid, is generated by the fetus's developing urinary system. The bladder holds urine as a neonate. The bladder comes from the urogenital sinus, which came from the cloaca. The bladder is therefore from the gut tube and is mesoderm. The filtration unit, be it pronephros, mesonephros, or metanephros, comes from mesoderm. We're going to use the words mesoderm and mesenchyme in this lesson. Mesoderm is the middle layer of the embryo that becomes everything not skin (ectoderm) and not gut (endoderm). Mesenchyme is undifferentiated tissue that is derived from the mesodermal layer.

Let's dive into the details of each stage of development before engaging congenital defects.

The Details: Weeks 1–2, Pronephros

The pronephros is just the template. Tubules grow, canalize, then disappear. The template needs to exist in order for the mesonephros to form. But once the mesonephros starts forming, the pronephros's job is complete, and it just disappears. The pronephros doesn't become anything, doesn't do anything, and there are no medical conditions associated with it. Know that it exists, recognize the word, but also don't learn anything about it.

The Details: Week 3–5, Mesonephros

The **mesonephros** is the functional filtration system of the developing fetus. There are two mesonephroses, one on each side of the fetus, just as there will be two kidneys on either side of the neonate. The mesonephros does not become the kidney, however. The mesonephros is the main excretory organ of adult aquatic vertebrates (fish). More evolved organisms (birds, mammals, us) use the mesonephros during embryogenesis while the kidneys are developing. The mesonephros is enormous relative to the size of the fetus, extending as long as the gut tube. The mesonephros is derived from **mesoderm** (meso derm + nephro n = mesonephros). The mesonephros comprises functional units that filter blood. These filtration units drain into a tubule that drains the mesonephros into the developing bladder. That tubule is called the **mesonephric duct**. Visualize these things as two distinct entities—the mesonephros (does the filtering) and the mesonephric duct (carries the filtrate to the bladder). The reason to do this mental exercise is because the **mesonephros involutes** (becomes nothing, has no disease associated with it), while the **mesonephric duct persists** (details to follow).

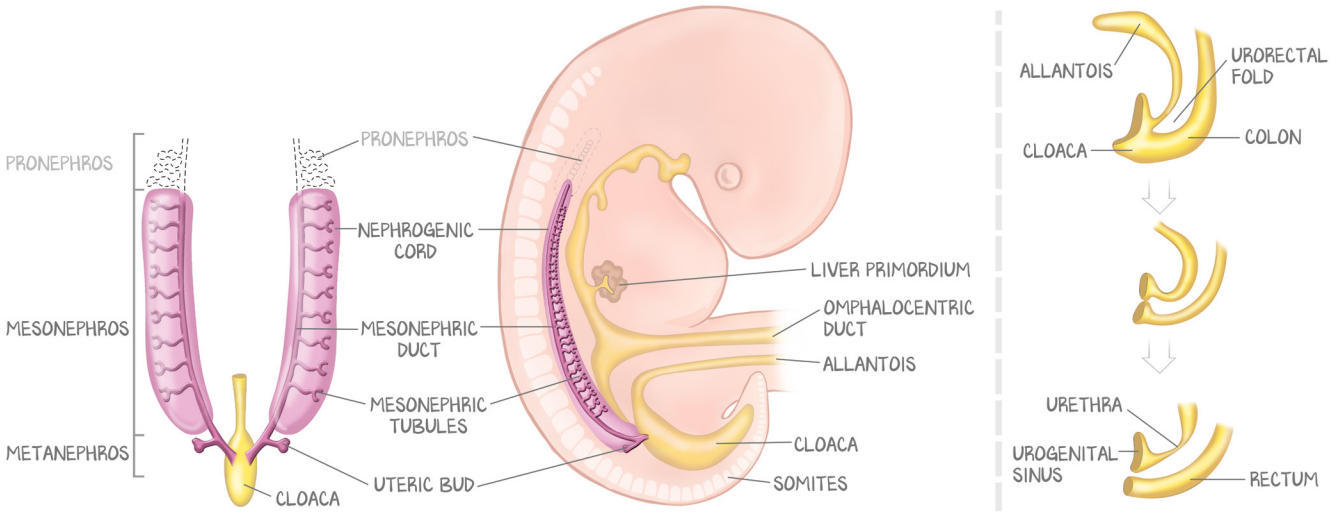


Figure 2.1: Mesonephros
On the left, an illustration of a single mesonephros, spanning cranial to caudal and draining into an endodermal cloaca. There is one mesonephros on each side, each mesonephros consisting of the filtration units and the mesonephric duct. Both mesonephric ducts drain into the cloaca. The common allantois drains out. On the right, the development of the gut tube, the cloaca, into a urogenital sinus and rectum, separated by the urogenital sinus.

The mesonephros drains into the embryonic bladder. That structure is derived from the gut tube. The **cloaca**, the common exit for water waste (urine) and solid waste (stool) is split by a urorectal fold, separating the cloaca into the **urogenital sinus** (bladder) and **rectum** (rectum). The mesonephric duct (mesoderm) drains the filtered fluid of the mesonephros (mesoderm) into the structure that stores water waste, the urogenital sinus (endoderm). Water waste is handled by the umbilical cord. The connection from the urogenital sinus to the umbilical cord is the **allantois**. The allantois does not become the urethra. This brief discussion of bladder embryogenesis is necessary for the next step in kidney formation.

The Specifics: Weeks 5–8, Metanephros

Right now in our progression through embryogenesis the mesonephros is filtering fluid, passing it down the mesonephric duct into the urogenital sinus, which drains to the umbilical cord through the allantois. The **metanephros**, what will be the kidney, is currently just an undifferentiated mass of mesenchyme called the **metanephric mass**. In order for the metanephric mass to become kidney, it must be penetrated by a tubule structure called the ureteric bud.

The **ureteric bud** originates from the distal end of the mesonephric duct. The ureteric bud will become the ureter, thus its name. But the ureteric bud will become more than that. The ureteric bud will become the **ureters**, **renal pelvis, and calyces,** and will contribute the **collecting ducts** to the renal medulla. The ureteric bud grows off from the mesonephric duct. At first, they share a common entry to the urogenital sinus. As time progresses, they separate from one another. Only the ureteric bud-derived structures will continue to become the urinary system.

As soon as the ureteric bud arises, you should start thinking of the mesonephric ducts as two things: the ureteric bud and the Wolffian duct. What is commonly taught is that the distal end of the mesonephric duct becomes the trigone of the bladder and ureter. Only sort of. We suggest a different perspective. While technically connected at first, that distal portion of the mesonephric duct that will become the trigone of the bladder is the same portion of mesonephric duct that the ureteric bud comes from, and will be the portion of mesonephric duct that becomes the ureter. So, just call that the ureteric bud. The second structure the mesonephric duct becomes is the **Wolffian duct**. Again, while

technically continuous with the cloaca and the ureteric bud at first, the Wolffian duct continues to drain the mesonephros into the urogenital sinus. In males, the Wolffian duct becomes the epididymis, vas deferens, and seminal vesicles. In females, the Wolffian duct involutes. In both males and females, the ureteric bud becomes the trigone of the bladder. Under our model of instruction, the Wolffian duct is a separate and distinct structure from the ureteric bud, even though they are derived from the same structure (the mesonephric duct).

The ureteric bud grows out from the urogenital sinus towards the **metanephric mass** (mass, mesenchyme, and blastema are all synonyms). As the ureteric bud penetrates the metanephric mass, it induces the mesenchyme to differentiate into **cortex.** The metanephric mass will form the renal columns, the capsule, and the **nephrons**. The nephrons comprise the glomerulus, proximal tubule, distal convoluted tubule, and loop of Henle. The metanephric mass is therefore actually all of the cortex, the renal columns of the medulla, and some of the straight tubules of the medullary pyramids. The collecting ducts, which are derived from the ureteric bud, act as the scaffolding for the developing straight tubules of the nephrons. The straight tubules give the foundation for the convoluted tubules. Multiple nephrons will empty their distal convoluted tubules into one collecting duct. The collecting ducts are there first, awaiting connection from DCTs and informing the construction of the loops of Henle. Some nephrons construct deep loops of Henle (juxtamedullary nephrons) and some construct shallow loops of Henle (cortical nephrons).

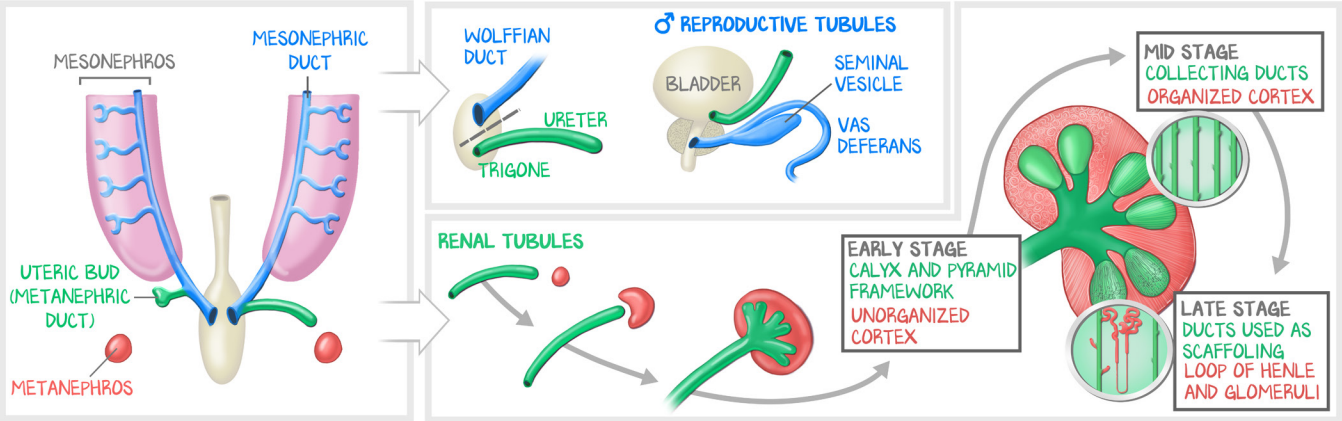


Figure 2.2: Metanephros
The ureteric bud develops from the distal end of the mesonephric duct, effectively separating the mesonephric duct into the Wolffian duct and ureteric bud. The mesonephros will involute and the Wolffian duct will become the male tubular reproductive organs. The ureteric bud migrates, penetrates, and stimulates the nearby metanephric blastema. The ureteric bud becomes the ureters, calyces, and collecting ducts of the medullary pyramids. The metanephric blastema becomes all of cortex and part of the medulla- the renal columns and the loops of Henle.

The mesonephros begins degenerating around week 8 as the metanephros takes over. While nephron maturation continues even after birth, the changes induced in the metanephric mesenchyme by the ureteral bud is sufficient to take over filtration. The mesonephros involutes. The mesonephric duct, now the Wolffian duct, involutes in females or becomes male reproductive tubules.

Kidneys' Ascension and Vascularization

Around week eight, the **long axis of the fetus grows**. The metanephric mass was located very near the cloaca, at the tail end of the fetus. The kidneys are supposed to be under the liver and spleen, quite a distance away from the rectum and urethra. As the fetus grows in length, the **kidneys ascend** into the **retroperitoneum**. As they ascend, the ureteric bud continues to lengthen, forming the ureters. The kidneys vascularize, gaining renal arteries that arise from the **aorta**.

Congenital Defects

Memorizing these diseases is not hard. The embryology is. We are going to draw on the embryology to explain why these disorders do what they do. This could be a short lesson where we just list the features of the disease—but that wouldn't help you learn it.

Hydramnios

Amniotic fluid **is fetal urine**. The fetus swallows amniotic fluid, and what stays in the fetal intestinal tract becomes fetal stool, called meconium. Fluid enters baby in two places—the mouth and the umbilical cord. The fetus **swallows amniotic fluid** and the intestinal tract absorbs water and the **placenta** provides perfusion by arteries. Fluid leaves baby in two places—the urethra and the umbilical cord. The fetal kidneys produce **fetal urine** (which is amniotic fluid), and the **placenta** has a venous drainage.

Amniotic fluid acts as a **cushion** for baby, to allow the structures to develop free of external compression.

Polyhydramnios means **too much amniotic fluid**. Too much amniotic fluid means not enough amniotic fluid is being swallowed. Polyhydramnios is a product of **intestinal obstruction**, a failure of intestinal development.

We're going to focus on the urine part—oligohydramnios (too little).

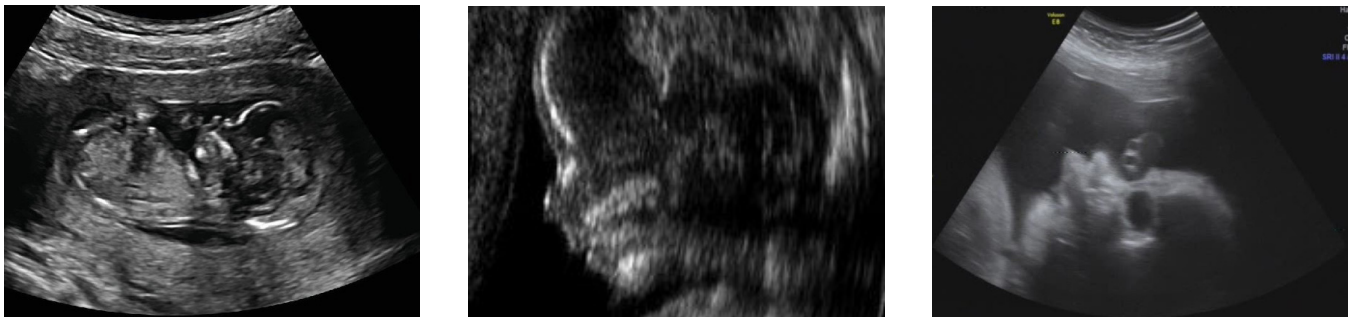
Oligohydramnios means **too little amniotic fluid**. Too little amniotic fluid means not enough fetal urine. Oligohydramnios is a product of **dysfunctional kidney development**. It also causes a loss of the cushion, so baby will get smooshed. If there is only moderate oligohydramnios, the baby gets a little smooshed (and usually is clinically asymptomatic). If there is severe oligohydramnios, as occurs when neither kidney forms, the baby gets smooshed a lot (as discussed in the next section).

Bilateral Agenesis of the Kidneys

The fetal kidneys filter blood delivered by the placenta. The fetal kidneys filter swallowed amniotic fluid. The fetal kidneys also **make amniotic fluid**. If there is complete agenesis of the kidneys, that is, there are no kidneys, then there **can't be any amniotic fluid**. But remember that until week eight, the mesonephros is the filtration unit. So some amniotic fluid was made. The mesonephros involutes regardless of whether the metanephros forms. Said more accurately, BOTH mesonephroses will involute regardless of whether two, one, or zero kidneys develop. If neither kidney develops, no more amniotic fluid is made, and the fetus gets smooshed a lot.

This is **Potter's sequence**, a sequence of logical steps that ends in the syndromic presentation. If there are no kidneys, then there is no amniotic fluid. If there is no amniotic fluid, then there will be no cushion. If there is no cushion, baby gets smooshed. Have a friend put a sheet over their face, then holding the sheet firm, have them push into the sheet. In this example, your friend's face being pushed against the sheet has a skull and a formed face, so the sheet conforms to your friend's face. But a fetus DOESN'T have a skull or a fixed face. So, the "sheet" doesn't conform to the shape of the fetus, the fetus conforms to the shape of the sheet. Smooshed. As the fetus's face grows into the pressure exerted by mom's internal organs and pelvis, the things that protrude from a face won't be allowed to do that. That means when baby's nose and chin have their growth limited, there will be a **flattened nose** and **recessed chin**. The face is smooshed back, so the **ears are rotated posteriorly**.

But oligohydramnios does not impact the face alone. Talipes equinovarus is how we say **clubfoot**. The feet (and the hands, but learn the feet) consist of the ankle (talus) and foot (pes) bent inward like a horse (equino) heel (equino). These structures are compressed, and move with upward rotation (varus). Thus talipes equinovarus is just a combination of words that describes clubfoot. The syndrome, therefore, is a combination of flattened nose, recessed chin, posteriorly rotated ears, and club feet.



(a) (b) (c)

Figure 2.3: Hydramnios
(a) Ultrasound at 20 weeks' gestation showing oligohydramnios. (b) Ultrasound at 20 weeks' gestation showing a normal amount of amniotic fluid. (c) Ultrasound at 20 weeks' gestation showing polyhydramnios.

We've discussed Potter's sequence in line with bilateral agenesis of the kidney because bilateral agenesis of the kidney results in the most severe form of oligohydramnios and presents with the most severe syndrome of Potter's sequence. There are other causes of oligohydramnios that result in a less severe form of Potter's sequence.

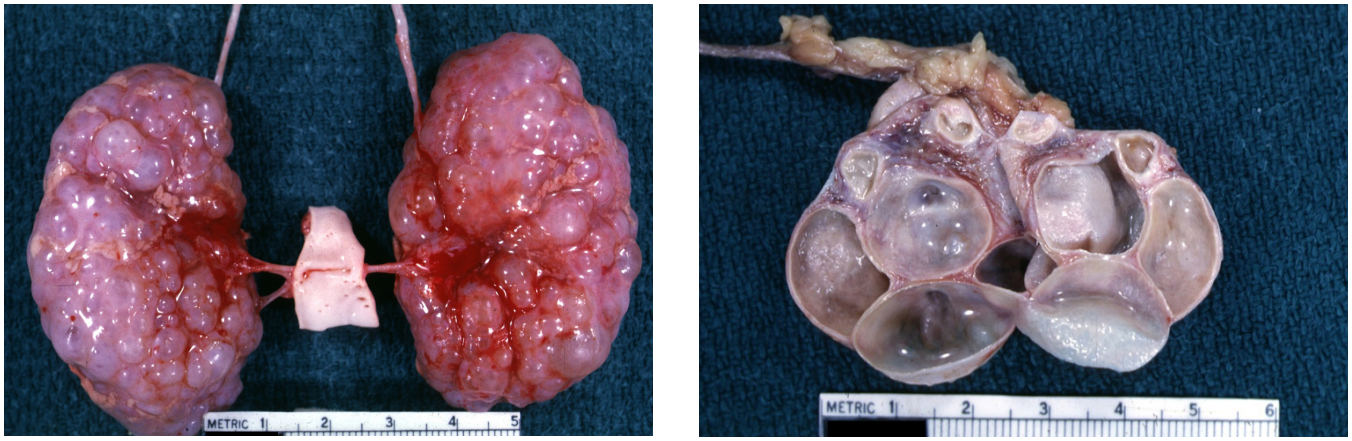
With bilateral agenesis of the kidney, there is an additional symptom to the syndrome. Kidneys are required for life—processing toxins like BUN, managing electrolytes, and maintaining fluid balance. If the oligohydramnios is because of absent kidneys, as soon as the fetus is born, as soon as the placenta isn't doing the majority of waste processing, the neonate can't regulate fluid or electrolytes. **No kidneys means no life.** Bilateral agenesis of the kidneys is incompatible with life outside the womb. While transplant could technically save a neonate, it is extremely difficult to find a kidney that would fit inside a neonate, especially one with growth restriction because of the oligohydramnios.

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

ARPKD is a disease caused by a specific genetic mutation, which results in both kidneys failing to form. The metanephric mass is penetrated by the ureteric bud, but the differentiation does not result in kidneys, but instead cysts. This disease is caused by a mutation in the **PKHD1** gene. In this disease, bilateral fetal kidneys are replaced almost entirely by cysts. These cysts are **elongated radial cysts** which are arranged **perpendicular to the capsule**. On gross section you will see a **sponge-like** kidney. The patient presents just as described above in bilateral agenesis of the kidney—severe oligohydramnios, Potter's sequence, and incompatibility with life outside the womb.

Even if a transplant is available for a neonate with ARPKD, even if they survive the first few days of life, extrarenal manifestations of the PKHD1 gene mutation result in **cysts in other places**. Specifically, the cysts occur in the **liver**, eventually leading to **hepatic fibrosis**, resulting in **cirrhosis** in childhood. To be clear, if the infant survives infancy with a renal transplant, dysfunction of other organs, such as the liver, will turn fatal in early childhood.

Therefore, you won't see a patient with ARPKD, because they die. What becomes important is genetic counseling of the parents who had a child with ARPKD, as they are both carriers for the autosomal recessive disease. What becomes important for licensure is recognizing the numerous elongated radial cysts on autopsy.



(a) (b)

Figure 2.4: Congenital Cystic Disease
(a) The many peripherally or radially oriented small cysts found in autosomal recessive polycystic disease. (b) The few, but large in number, cysts of cystic renal dysplasia.

Unilateral Agenesis of the Kidney

When **one kidney fails to grow**, the other one **picks up the slack**. These patients, very much unlike their bilateral agenesis counterparts, are most often **asymptomatic**. The presence of a **unilateral agenesis** is often found on routine imaging for something else. Abdominal imaging is obtained for some other reason, and one of the kidneys isn't where it's supposed to be AND it isn't somewhere else (compare this to horseshoe and ectopic kidneys, coming up). The good kidney does undergo **hypertrophy** in utero, which means that it just has more ducts, more nephrons, more cortex and medulla. Because of this hypertrophy, **urine volume**, **plasma clearance**, and **filtration** are **all normal**.

But what causes agenesis? There are two mechanisms. The first is **failure of the ureteric bud** to form in the first place. This defect must happen very early on in development, around week 3. The mesenteric mesenchyme is never penetrated by the ureteric bud, so cannot be induced to make a kidney. In addition, the ureteric bud never forms, so the ureter will not form either. In the second version of this disease, the ureteric bud forms and penetrates the metanephric mesenchyme, yet still **fails to induce differentiation**. In this case, the ureteric bud forms and migrates, so the ureter is present in the neonate, but the kidney still never forms. This second type, where the ureteric bud fails to induce differentiation, is called **multicystic renal dysplasia**. Unlike ARPKD which has numerous small cysts that entirely replace the kidney, multicystic renal dysplasia demonstrates few, enormous cysts. On histology, the characteristic feature is presence of undifferentiated mesenchyme.

For test-taking, use caution when reading vignettes. Multicystic renal dysplasia has undifferentiated mesenchyme, with some mature glomeruli and tubules, and is in a kidney with enormous cysts. Wilms' tumor, also seen in children, will also have undifferentiated mesenchyme in the histology report. Wilms' tumor, however, will have aborted or immature tubules, no glomeruli, and will be found in a kidney with a tumor, not a cyst.

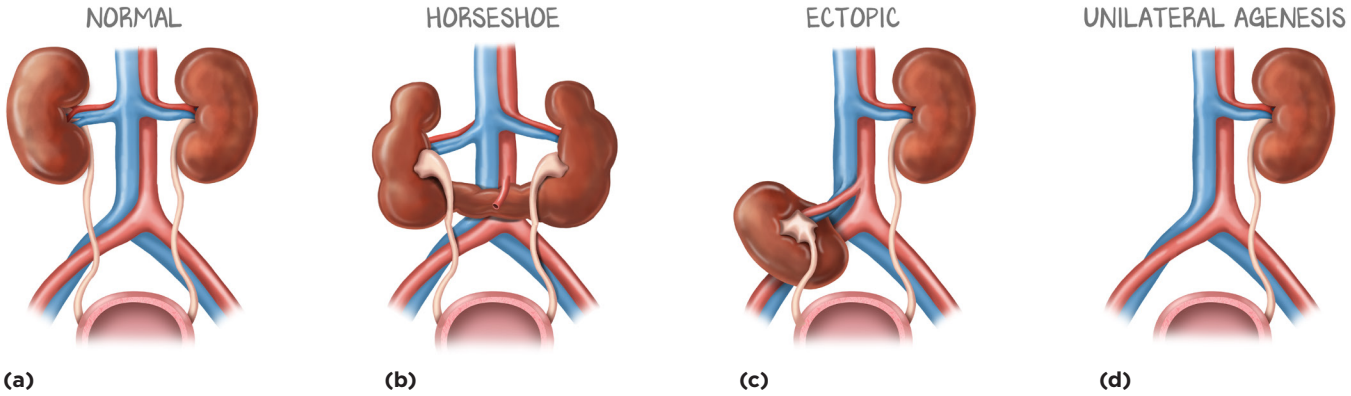


Figure 2.5: Congenital Defects of Kidney Location
(a) Normal. (b) Horseshoe. (c) Ectopic. (d) Unilateral agenesis of the kidney.

Horseshoe Kidneys

There are two kidneys in the adult human. These two kidneys form from two separate metanephric masses. Each metanephric mass is penetrated by its own ureteric bud. At the time that penetration happens, the fetus is still very small, and those metanephric masses are very close together. As they mature, differentiate, and proliferate, the two masses can bump into each other, resulting in **fusion of the two kidneys**. This happens at the **lower pole** (90%) far more often than at the upper pole (10%). As the kidneys ascend and get vascularized, they are on opposite sides of the aorta. They are supposed to rise and spread out to the flanks. But as fused kidneys ascend, they cannot spread out, and that fused lower pole ascends at midline. As the two kidneys connected across midline rise along the aorta, that midline connection piece can get stuck on the aorta or the superior mesentery artery.

The kidneys both function. They just aren't where they are supposed to be. If imaging reveals absent kidneys in an asymptomatic patient, the radiologist need only look down towards the feet. If radiology sees two kidneys with a connection across midline, it's a horseshoe kidney (compared with ectopic and agenesis). The real problem with horseshoe kidneys is that they are **predisposed to renal calculi and pyelonephritis** because of the stagnant urine in the fused segments. Horseshoe kidney has **normal kidney function** and is **the most common congenital abnormality** (1 in 600).

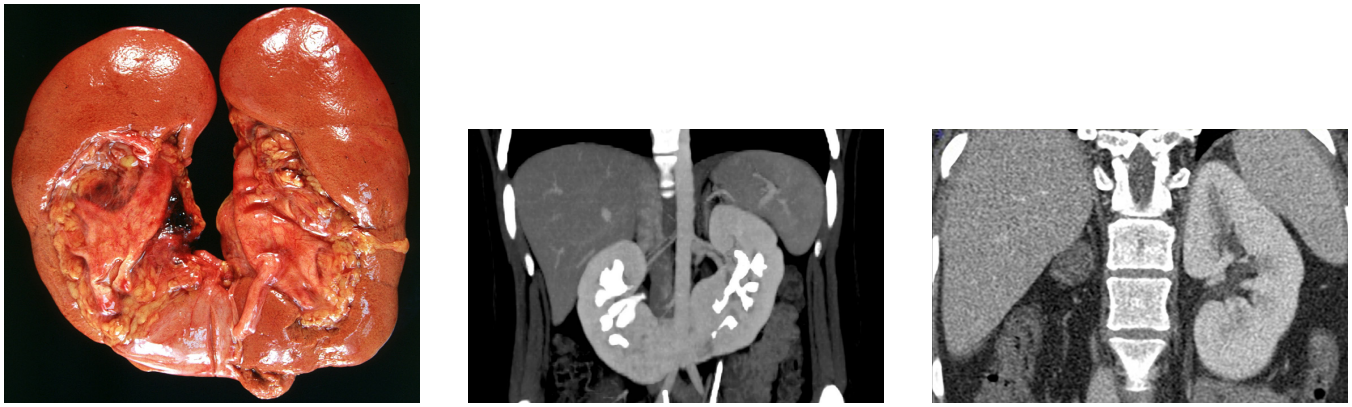


Figure 2.6: Radiography of Kidney Location
(a) Gross anatomy of a horseshoe kidney. Notice the fused inferior pole. (b) Coronal CT demonstrating a horseshoe kidney. (c) Coronal CT showing an ectopic kidney with a radiofinder image nearby.

Ectopic Kidneys

The normal development of the kidneys involves the ascension of the kidneys from the pelvis into the retroperitoneal space of the upper abdomen. This ascension is compensated for by **elongation of the ureters**. If the ureters didn't elongate, the tubules would snap apart as the kidneys and bladder grew away from each other. But it isn't the "being tugged on" that induces the ureters to grow loner. The **elongation of the tubule happens regardless** of whether the kidney ascends or not. So, if the kidneys ascend and the elongation happens, the ureters are the right length. But if the kidney doesn't ascend and the elongation of the ureters happens as if it did ascend, the ureters have extra length for where the kidney is. With extra length of a floppy tube extra length in a floppy tubule, it bunches up, and its path is **tortuous**. A tortuous path is more prone to obstruction and urine stagnation, and therefore **pyelonephritis**. The most common ectopic site is **in the pelvis**—where the kidney starts as a metanephric mass.

Most patients are asymptomatic. The way this will present is in a patient with a CT scan of the abdomen for something unrelated to the kidney. There is a "missing kidney." Whereas agenesis of the kidney presents with a missing kidney that cannot be found, and horseshoe kidney presents with missing kidneys that are found connected, ectopic kidneys present with a missing kidney that can be found by scanning a little farther down.

Hypoplastic Kidneys

Agenesis of a kidney is where one kidney just doesn't form. Those patients had normal renal function. A hypoplastic kidney is a kidney that develops, just more meagerly than normal. These patients also have normal renal function. Kidneys that fail to develop fully are little kidneys. Little kidneys have a ureter. Little kidneys work. But little kidneys are **smaller in weight**, and have **fewer pyramids** (< 6) and **fewer calyces** (< 6). Disease can cause hypoplastic kidneys. As a kidney dies, as chronic kidney sets in because of diabetes or hypertension, the normal kidney gets scarred, and becomes small. Because the congenital hypoplastic kidney is rarely found in childhood (the other kidney can compensate with hypertrophy), the question often becomes, "*is this hypoplastic kidney congenital, or a because of a disease process?*" Congenital hypoplasia will be found **without comorbid disease** and **without scarring**, whereas an adult pathogenically hypoplastic kidney WILL have scarring and a disease state that predisposed the kidney to injury.

THE THING	WHAT IT DOES OR BECOMES
Pronephros	Weeks 1–2, probably helps mesonephros form
Mesonephros	Functional filtration unit from weeks 3–8, from mesoderm Consists of "embryonic glomeruli" that filter, and mesonephric duct that drains Drains into urogenital sinus
Mesonephric duct	Drains mesonephros to the urogenital sinus, so is from mesoderm Most of duct becomes Wolffian duct (involutes in females; male reproductive tubules) Distal duct becomes ureteric bud
Ureteric bud	Derived from distal mesonephric duct, so is from mesoderm Becomes the ureter, pelvis, calyces, and collecting ducts in medulla Migrates to metanephric blastema and induces differentiation into cortex
Metanephric mesenchyme	Mesodermal mesenchyme, undifferentiated tissue that will be cortex Induced to differentiate into cortex, renal columns, and nephrons Uses collecting ducts from ureteric bud as scaffolding for loop of Henle

Table 2.1: Mesodermal Structures Become Kidney and Ureters

THE THING	WHAT IT DOES OR BECOMES
Cloaca	Common exit for water waste and solid waste Is separated into urinogenital sinus and rectum by urogenital fold
Urogenital sinus	Common structure that will become bladder and urethra Urogenital sinus drains out through allantois Mesonephric duct drains into urogenital sinus early in development Ureteric bud, the ureter, drains into a more developed urogenital sinus later in development
Allantois	Drains urogenital sinus to umbilical cord

Table 2.2: Endodermal Structures Become Bladder and Urethra (more on this in Bladder #1: *Bladder*)

DISEASE	CHARACTER
Bilateral agenesis of kidneys	Renal kidneys make urine; fetal urine = amniotic fluid **Potter's sequence** (no kidneys → oligohydramnios → crushed fetus → Potter's facies, talipes equinovarus **Potter's facies** = flattened nose, posteriorly rotated ears, recessed chin **Talipes equinovarus** = talus (ankle), pes (foot), equinovarus (inward rotation) = **clubfoot** Without any renal function, **incompatible with life**
Autosomal recessive polycystic kidney disease	*Patient*: At birth, **infant**; overt **renal failure** = **fatal** *Path:* Autosomal **recessive**, mutation of **PHKD1** *Gross:* Bilateral kidneys, many **small** cysts, **radial** and **elongated**, **perpendicular** to capsule *Histo*: Complete replacement of kidney with elongated cysts**, no glomeruli** *Downstream:* Survivors develop cirrhosis and die in childhood
Multicystic renal dysplasia	*Patient:* At birth, **infant**; bilateral disease is the same as ARPKD, unilateral asx *Path:* Caused by failure of **metanephric differentiation** Gross: Very few, very large, circular cysts *Histo*: circular cysts surrounded by **mesenchyme**
Horseshoe kidney	**Fusion** of the kidneys either at the upper pole (10%) or the **lower pole** (90%) As they ascend they get caught on the **inferior mesenteric artery** Normal function of kidneys, but may lead to **increased risk of stone formation**
Ectopic kidneys	Normal = The kidneys develop in the pelvis, then ascend to their location Ectopic = **Failure to ascend**, developing usually **within the pelvis** or at the **pelvic brim** Tortuous ureters cause increased risk of obstruction, stagnation → **pyelonephritis**
Hypoplasia	A truly hypoplastic kidney, that is, one that **did not fully develop**, will be **small**, have **fewer than 6 pyramids**, and **no signs of scarring**, vs. a normal kidney that shrank from fibrosis or HTN.

Table 2.3: Congenital Diseases of the Kidney